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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 09/920,033 | 08/01/2001 | Rosanne M. Crooke | ISPH-0592 | 5785 |

72984 7590 01/07/2009

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| EXAMINER | |
|---|---|
| EPPS FORD, JANET L | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1633 | |

| MAIL DATE | DELIVERY MODE |
|---|---|
| 01/07/2009 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/920,033 | CROOKE ET AL. | |
| | Examiner | Art Unit | |
| | Janet L. Epps-Smith | 1633 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *07 August 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1,8-10,12,13,20,28-30,33-35 and 40-43* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,8-10,12,13,20,28-30,33-35 and 40-43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

**DETAILED ACTION**

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

2. Claims 1, 8-10, 12-13, 20, 28-30, 33-35 and 40-43 are presently pending for examination.

***Claim Rejections - 35 USC § 103***

3. Claims 1, 8-10, 12-13, 20, 28, 29-30, 33-35, and 40-43 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Rouy et al. (US Patent No. 6,512,161; or WO 99/35241 A1; see IDS of 4-07-06; citations given for US Patent), and Eggerman et al. (See IDS of 4-06-05) in view of GenBank Accession No NM_000384 (Huang et al. Reference #1), Monia et al. (US 5,656,612; see Reference A of PTO-892 mailed 1/14/2003), Agrawal et al. (2000, see Reference U of PTO-892 mailed 1-13-2004), and Wengel et al. (US 2002/0068708A1), as applied to claims 1, 8-10, 12-13, 20, 28, 29-30, 33-35 above, and further in view of Bennett et al. (US 6,172,216), for the reasons of record.

Applicant's arguments filed 08/07/08 have been fully considered but they are not persuasive. Applicants traverse the instant rejection on the grounds that none of the cited references either alone or in combination, suggest the presently claimed invention.

Moreover, Applicants argue that they present evidence that the presently claimed antisense compounds exhibit greater than 80% and up to 100% inhibition of human apolipoprotein B expression. According to Applicants SEQ ID NO: 25, 43, 53 and 57 all exhibit greater than 80% and up to 100% inhibition of human apolipoprotein B

expression. However, Applicant's showing is no commensurate in scope with the claimed invention, which encompasses an exponential number of possible antisense compounds of 20 nucleobases in length targeting the well over 13,000 nucleotides. Applicant's showing is not sufficient to demonstrate unexpected results of inhibition of up to 100% inhibition of apolipoprotein B expression for the full scope of antisense compounds encompassed by the instant claims.

Moreover, Applicants again assert that Agrawal et al. teaches away from the claimed invention, and cites ¶ #1, col. 1 of page 77 to support this position. However, the sentence immediately following the passage referred to by Applicants, it states "*Our experience, however, shows that it is difficult to find a 20-nucleotide site that includes the initiation codon and satisfies all the criteria discussed in this review for optimal antisense oligonucleotide design.*" Therefore, there is no teaching away, since the instant claims do not include the start codon, and Agrawal et al. teaches that it is difficult to design antisense targeting the start codon. Moreover, this reference also teach that other preferred sites, such as the 5' and 3' UTR, the coding region, and intron/exon junctions are also useful for designing antisense compounds.

4. As stated in the prior Office Action, one of ordinary skill in the art seeking to further understand the role of apolipoprotein B gene expression in cellular processes, would have been motivated to design antisense oligonucleotides targeting the mRNA encoding the apolipoprotein B gene as defined by SEQ ID NO: 3 of the instant specification, since GenBank Accession No. NM_000384 clearly set forth the nucleotide sequence of SEQ ID NO: 3 as the sequence encoding the full-length apolipoprotein B

mRNA. Moreover, NM_000384 clearly defines the 5'-UTR as occurring before nucleotide 129, start codon region as beginning at nucleotide 129, and the coding sequence as extending from nucleotide 129 to nucleotide 13820, therefore the 3' UTR would be defined as the remaining sequence corresponding to nucleotides 13821 through 14121. Moreover, according to Agrawal et al., if the nucleotide sequence of a gene was known, designing antisense oligonucleotides to target the various regions of that gene, including the 5' UTR, *specifically nucleotides 1-128 of SEQ ID NO: 3,* the coding sequence, *which extends from nucleotide 129 through 13820 of SEQ ID NO: 3,* and the 3' UTR, nucleotides 13821 through 14121 of SEQ ID NO: 3, as suggested by Agrawal et al., would allow the ordinary skilled artisan to further elucidate the role of a target gene of interest (apolipoprotein B, as suggested by Eggerman et al. and Rouy et al.) in various cellular processes.

One of ordinary skill in the art would have been motivated to design compounds of 12 to 30 nucleobases in length since Rouy et al. expressly teaches antisense oligonucleotides targeting apolipoprotein B mRNA comprising at least 20 nucleobases in length. Moreover, one of ordinary skill in the art would have been motivated to design oligonucleotide compounds targeting apolipoprotein B mRNA comprising one or more sugar modifications, phosphorothioate modified internucleoside linkages, and 5'-methylcytosine modified nucleobases, since Monia et al. teaches that these modifications are known to both increase hybridization efficiency and nuclease resistance of oligonucleotide compounds comprising these modifications. Moreover, Monia et al. teach that oligonucleotides comprising these modifications possess high

target site specificity and increased cellular uptake in comparison to unmodified antisense oligonucleotides. Furthermore, one of ordinary skill in the art at the time of the instant invention would have been motivated to make this modification since the prior art teaches that antisense compounds comprising LNA modifications produces antisense compounds with stability towards exonucleolytic degradation, effective delivery into cells, and display unprecedented binding affinity to both RNA and DNA (see Wengel et al., page 3, lines 25-35).

It would have been obvious to the ordinary skilled artisan to combining prior art elements of Monia et al., Agrawal et al., and Wengel et al. with the teachings of Rouy et al. and Eggerman et al. according to known methods to yield predictable results, specifically to protect the modified antisense oligonucleotides of Rouy et al. and Eggerman et al. from nuclease degradation, increase hybridization efficiency, and increase cellular uptake of the modified antisense oligonucleotide.

5. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Epps-Smith whose telephone number is 571-272-0757. The examiner can normally be reached on M-F, 10:00 AM through 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

*JLE*
*/Janet L. Epps-Smith/*
*Primary Examiner, Art Unit 1633*

| Application Number | Application/Control No. | Applicant(s)/Patent under Reexamination | |
|---|---|---|---|
| | 09/920,033 | CROOKE ET AL. | |
| | Examiner | Art Unit | |
| | Janet L. Epps-Smith | 1633 | |